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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/837,560	04/18/2001	Betsy M. Sutherland	BNL-2019	7529

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EXAMINER	
CLOW, LORI A	
ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/837,560	SUTHERLAND, BETSY M.	
	Examiner	Art Unit	
	Lori A. Clow, Ph.D.	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-31 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-31 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

Claims 1-31 are currently pending.

Information Disclosure Statement

The IDS, filed 13 August 2001 has been entered and considered. An initialed copy of the form PTO-1449 is included with this office action.

Claim Rejections - 35 USC § 112

Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, step (e) recites "calculating the frequency of clustered damages ($_c$) in the DNA to be assayed.." This is unclear because there is no definition of ($_c$) in the specification and it appears that a symbol is missing. Please correct to read (Φ_c), if this is what applicant has intended.

Claims 4 and 20 are confusing for denoting the steps (a) and (b). Since these claims are dependent upon claims that already recite steps (a)-(e) and (a)-(c), respectively, it is requested that applicant change the further steps to (i) and (ii).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

Claims 25-27 and 31are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting and quantifying clustered damages in DNA due to ionizing radiation, does not reasonably provide enablement for detecting and quantifying clustered damages due to a chemical agent such as a chemical carcinogen or a chemotherapeutic agent . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The specification discloses the methods of the current invention in terms of applicability to ionizing radiation. The first example, at page 17, beginning line 21, recites comparisons between DNA that has been irradiated verses DNA that is untreated. This is illustrated in Figure 2. Figure 3 also illustrates an electronic image of a representative agarose gel for damage cluster analysis in which the samples have been irradiated with X-rays and γ-rays. In fact, all of the examples and figures relate to damage caused by ionizing radiation and not caused by chemical agents. The state of the prior art indicates that there is a clear difference

between damage induced by ionizing radiation and that induced by chemical agents. For example, Prise et al (Carcinogenesis (1999) Vol. 20, No. 5, pages 905-909: PTO-1449 reference AT2) state

"DNA can be damaged by a range of oxidative reagents and, in the cellular situation, it is continually being oxidatively damaged by normal cellular processes (1). For ionizing radiation, damage is predominantly produced by OH radicals (2). A key difference between ionizing radiation-induced damage and that produced by other chemical oxidizing agents is that a range of damage products are produced and these are locally clustered on the DNA."

Therefore one of ordinary skill in the art would not know how to practice said invention with regards to detecting and quantifying clustered damages in DNA caused by chemical agents, as no parameters are given for application of the chemical agent to said DNA. Neither the instant specification nor the prior art provide guidance for detecting the "range of damage products" using the claimed method steps, therefore it would require undue experimentation by one skilled in the art to detect clustered DNA damage incurred by chemical agents. For these reasons, these claims are not enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-23 are rejected under 35 U.S.C. 102(a) as being anticipated by Sutherland et al. (PNAS (2000) Vol. 97, No. 1, pages 103-108).

Sutherland et al. teach a method of quantitating clustered damages in genomic DNA as set forth in claim 1 by the following steps:

(a) providing a sample of DNA (page 103, column 2, Methods),

(b) contacting the DNA with a lesion-specific cleaving reagent (page 103, column 2, lines 8-13; page 106, column 1, lines 1-27),

(c) and (d) quantitatively determining the number average molecular length (Ln) of double stranded DNA (page 103, column 2, lines 14-17) and,

(e) calculating the frequency of clustered damages by $\Phi_c = 1/L_n$ (+enzyme) – $1/L_n$ (-enzyme) (page 104, column 1, equation 2).

Sutherland et al. teach the method wherein the DNA is from a biological organism and is genomic DNA which has been exposed to ionizing radiation (page 104 and Figure 1) thereby anticipating claims 2, 3, 19, and 28-30.

The method of determining the average molecular length, as in claim 4, is taught at page 103, column 2 to page 104 column 1.

The various lesion-specific enzymes of claims 5-18 are taught at page 103, column 2, Methods section; page 104, Table 1; page 105 Figure 2; and page 106, Figure 3.

DNA damaging agents such as radon (page 103, column 1), x and γ rays (page 105) are also taught, which anticipates claims 21-23.

Claims 1-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Freeman et al (Analytical Biochemistry (1986) Vol. 158, pages 119-129: PTO-1449 reference AR2).

Freeman et al. teach an agarose gel electrophoresis method for quantitating single strand breaks in nonirradiated DNA. In this method the number of average molecular lengths and

length of average molecular lengths can be computed (page 122, column 2). Further, the frequency of the breaks can then be determined by comparison of the corresponding average molecular lengths of DNAs treated and not treated with inducing agents such as radiation, chemicals, or lesion-specific endonucleases (see abstract; Methods section; page 122, equation 13). In this method DNA is treated with an endonuclease from *M. luteus,* which specifically and quantitatively makes single strand nicks at each pyrimidine dimer (page 123, column 1, lines 19-25).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-24 and 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freeman et al (Analytical Biochemistry (1986) Vol. 158, pages 119-129: PTO-1449 reference AR2), in view of Wallace (Radiation Research (1998) Vol. 150 (Suppl. 5), pages S60-S79: PTO-

1449 reference AT), in further view of Sutherland et al. (PNAS (2000) Vol. 97, No. 1, pages 103-108).

Freeman et al. teach an agarose gel electrophoresis method for quantitating single strand breaks in nonirradiated DNA. In this method the number of average molecular lengths and length of average molecular lengths can be computed. Further, the frequency of the breaks can then be determined by comparison of the corresponding average molecular lengths of DNAs treated and not treated with inducing agents such as radiation, chemicals, or lesion-specific endonucleases (see abstract; Methods section; page 122, equation 13). In this method DNA is treated with an endonuclease from *M. luteus,* which specifically and quantitatively makes single strand nicks at each pyrimidine dimer (page 123, column 1, lines 19-25).

Freeman et al do not teach the use of Fgp protein glycosylase or the use of the specific endonucleases III and IV from *E. coli.* However, Wallace does teach Fgp protein, endonuclease III and endonuclease IV as lesion-specific enzymes that play a crucial role in DNA repair (see entire review article; see abstract). It would have been prima facie obvious to one of ordinary skill in the art to utilize the enzymes of Wallace in the methods of Freeman et al., who acknowledges that quantitation of other lesions in DNA can be detected by this method, for example detection of lesions using endonuclease III from *E. coli* (page 128, column 2, lines 28-37).

Freeman et al. and Wallace et al. do not teach this method as applicable to a whole organism, however, Sutherland et al. do teach that their methods are prime for investigations of biological organisms (page 107, column 2, lines 33-37). It would have been prima facie obvious to one of ordinary skill in the art to use the methods of Freeman and Wallace to detect clustered

DNA damage in an organism (claims 19-24 and 28-31) where the motivation is supplied by Sutherland who states that their approach provides the foundation for correlating clustered lesions induced by ionizing radiation in cells, tissues, or organisms.. (page 107, column 2).

No claims are allowed.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242, or (703) 308-4028.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (703) 306-5439. The examiner can normally be reached on Monday-Friday from 10am to 6:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward, Ph.D., can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Legal Instrument Examiner, Tina Plunkett, whose telephone number is (703) 305-3524, or to the Technical Center receptionist whose telephone number is (703) 308-0196.

MARJORIE MORAN
PATENT EXAMINER

August 21, 2003

Lori A. Clow, Ph.D.
Art Unit 1631